Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Editorial overview: Engineering and design

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Sarel Fleishman is an Associate Professor at the Weizmann Institute of Science (Israel) and serves as director of its Dr. Barry Sherman Institute for Medicinal Chemistry. The Fleishman lab develops general methods for protein design, including enzymes, antibodies and membrane proteins. Several of the lab's design algorithms, such as PROSS for stability design and FuncLib for function optimization, are implemented as web servers that are attracting thousands of academic users. These methods have led to dozens of publications and patent filings on optimized proteins for clinical or industrial use that were not amenable to optimization using conventional methods.

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Roy A. Mariuzza is a Professor at the University of Maryland Institute of Bioscience and Biotechnology Research (USA). Many structural studies from his lab have contributed to our knowledge of adaptive and innate immune recognition. These include structures of antigen–antibody complexes, of superantigens bound to TCR and MHC molecules, of NK cell receptors in complex with MHC and other cellular ligands, of peptidoglycan recognition proteins (PGRPs), of autoimmune TCRs bound to self-peptide–MHC, of tumor-specific TCRs in complex with cancer neoantigens, of TCRs bound to SARS-CoV-2 epitopes, and of lamprey variable lymphocyte receptors (VLRs).

The past decade has seen remarkable progress in protein engineering and design capabilities. New algorithms enable the design of new-to-nature proteins that can serve as binders, inhibitors, diagnostics, and as biologically active materials. In addition, our understanding and ability to engineer improved versions of sophisticated enzymes, antibodies and T cell receptors are opening new possibilities for "green" chemistry and therapeutics. Finally, the most remarkable development in structural biology of the past decade, the accurate prediction of protein structures and complexes using AI-based methods, is opening up previously unimaginable opportunities to characterize and optimize natural proteins.

The protein-engineering community's response to the coronavirus pandemic is a remarkable case in point for these improved capabilities. Hsieh and Maclellan review how the structure of SARS-CoV-2 spike glycoprotein was used to guide the design of improved immunogens for COVID-19 vaccines. The review also describes the development of multivalent protein nanoparticles displaying SARS-CoV-2 immunogens to augment neutralizing antibody responses.

In the future, inhibitors could be designed from scratch and on-demand to target emerging threats. Correia et al. review concepts and methods used over the past decade to *de novo* design binders to a range of targets. The field has seen remarkable progress in recent years, including *de novo* designed anti-coronavirus inhibitors. Still, there are critical unaddressed challenges: success rate is low, design mostly targets hydrophobic surfaces, and the designed proteins are overwhelmingly α helical, limiting their options to bind complex antigenic surfaces. These limitations will have to be overcome to make *de novo* binder design competitive with established methods.

Many natural proteins self-assemble to form filaments, capsids, and microcompartments. Self-assembly provides access to so-called functional materials, but it is complicated to change the geometrical and functional properties of naturally occurring self-assembled systems. As Ben Sasson and Wang explain, over the past decade, computational design has made huge progress in generating new assemblies, either starting from naturally occurring proteins or from de novo designed ones. The review explains how several breakthroughs in various protein design tasks were needed to enable these new possibilities. New designs include functional materials, such as superior vaccines and surfaces that interact with cells.

Structural and biochemical data are typically much easier to obtain for soluble proteins compared to transmembrane ones. Consequently, capabilities in membrane-protein design lag far behind those in soluble proteins. Lu and Zhu explain the principles for membrane protein folding and design and review recent progress in designing both small and large membrane scaffolds, as well as receptors with modified functionality. These capabilities may have broad implications for synthetic biology and biotechnology but successes are still rare. Advances in structure determination and prediction, such as cryo-EM and ab initio structure prediction with AlphaFold, may provide the data needed for accelerating progress in this critical field.

Societal sensitivity to energy and environmental impact is leading the chemical industry to consider enzymatic transformations instead of energy-intensive and polluting alternatives. Selective insertion of oxygen into organic molecules is a key step in the production of many chemicals and drugs. A recently discovered fungal enzyme family, called the unspecific peroxygenase (UPO) family, exhibits very diverse substrate selectivities. Like almost all natural enzymes, however, they do not meet industrial stringencies and must undergo significant improvement. Alcalde et al. describe their great potential and the combination of modern experimental and computational methods that are being implemented to quickly bring these enzymes into "real-world" use. As a family that has only been recently described, UPOs serve as a benchmark for measuring the progress that enzyme engineering has made relative to previously engineered monooxygenases, such as cytochrome P450.

Many natural enzymes and binding proteins are allosterically controlled, allowing a cell to sense and respond to changes in its environment. As Dokholyan et al. explain, our understanding how conformational changes are transmitted in proteins has substantially increased over the past decade as have engineering capabilities. Nevertheless, engineering allostery demands a fine balance between ligand binding, conformational change and protein stability, which can be mutually antagonistic. Ways to overcome these challenges will increase the scope and reliability of engineering methods.

Biosensors are a promising area for applying protein engineering to the development of probes and diagnostics for industrial or clinical use. Alexandrov et al. explain the principles used to construct platforms for sensing a variety of different ligands. A key problem is that natural receptors typically do not exhibit large conformational changes that can translate into substantial changes in readout. Thus, the dynamic range of most receptors is too small. They review recent studies that construct artificial receptors with a large dynamic range by fusing ligand-dependent dimerization domains and enzymes the produce the readout only upon dimerization. Despite progress in this field, commercial adoption is slow, requiring robust platforms that can be easily adapted to sense a variety of different ligands.

T cell receptor (TCR) immunotherapy is becoming a viable modality in cancer treatment with efficacy in clinical trials. Rosenberg and Baker review structure-based engineering efforts to design safe and efficacious TCRs for cancer immunotherapy. These strategies aim at enhancing TCR affinity for cancer-associated antigens while avoiding cross-reactivity with self-antigens that could lead to adverse clinical events.

Antibodies have now become the most important category of new drugs, including both proteins and small molecules. Deane et al. review how recent advances in protein structure prediction are leading researchers towards the ability to computationally design antibodies that bind tightly to defined antigens. These computational methods will complement traditional methods for antibody discovery, which are costly and time-consuming.

Metamorphic proteins possess the remarkable ability to reversibly interconvert between multiple well-defined structures (fold switching) that may have distinct functions. Dishman and Volkman describe efforts to identify natural metamorphic proteins, which may include as many as 4% of proteins in the PDB, and to design new fold-switching proteins *de novo*. Such proteins have applications as molecular switches, biosensors, and molecular machines.

Light-sensitive protein switches are engineered by genetically fusing natural light-sensitive protein domains with effector domains from other proteins. McCue and Kuhlman review recent developments in the emerging field of optogenetics, which include light-sensitive antibodies, voltage-sensing switches to control gene transcription, and tools for controlling protein localization within a cell.

Conflict of interest statement

Nothing declared.